Consecutive Reactions of Vinylic Phosphonium Salts with Grignard Reagents Catalyzed by CuBr−Ag_2CO_3 or CuBr−H_2O

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Received May 15, 1996

In recent years sequential transformations have attracted much interest because they provide a simple and efficient entry to complex compounds by including two or more transformations in a single operation to increase the complexity of a substrate starting from commercially available relatively simple precursors.[1] In our laboratory consecutive reactions of phosphonium salts have been developed as a general synthetic approach for polyfunctionalized fluoroalkenes,[2] fluoro enynes,[3] fluoro dienes,[4] and fluoro epoxides[5] which would be difficult to prepare otherwise.

The chemistry of vinylic phosphonium salts has attracted considerable interest since the β-addition of nucleophiles to the vinyl group is a convenient and synthetically useful reaction for the formation of new alkylidenephosphoranes which can be utilized as synthetic reagents, particularly for the synthesis of heterocyclic compounds.[6]

The reactions of vinyltriphenylphosphonium salts with alkyllithium and Grignard reagents have been reported, but both reactions proceed in poor yields.[7] It thus appears that as a synthetic method, the ability of the addition of organolithium and Grignard reagents to vinylic phosphonium salts to produce results is strictly limited. This limitation may be due to the basicity of those reagents.

Results and Discussion

We report that the consecutive reactions between Grignard reagents, vinylic phosphonium salts, and then aldehydes are catalyzed by CuBr−Ag_2CO_3 or CuBr−H_2O.

The reaction of a phenyl Grignard reagent with vinyltriphenylphosphonium bromide gave a red ylide solution. After addition of an aldehyde, triphenylphosphine but no alkene was obtained. The Grignard reagent acts as a base rather than a nucleophile under these conditions.

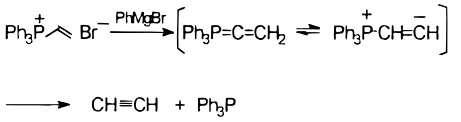


Table 1. Catalyzed Sequential Additions

run	R^1	R^2	additive[a]	yield of **4** (%)[b]
1	C_6H_5	4-$(CH_3)_2NC_6H_4$	CuBr	25
2	C_6H_5	4-$(CH_3)_2NC_6H_4$	Ag_2CO_3	0
3	C_6H_5	4-$(CH_3)_2NC_6H_4$	CuBr−Na_2CO_3	20
4	C_6H_5	4-$(CH_3)_2NC_6H_4$	CuBr−Ag_2CO_3	73
5	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	CuBr	20
6	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	CuBr−Ag_2CO_3	73

[a] All additives were dried before use. [b] Isolated yields.

Table 2. Reactions of Grignard Reagents with 1 Followed by Addition of 3 Catalyzed by CuBr−Ag_2CO_3

compd	R^1	R^2	yield (%)[a]	(*E*):(*Z*)[b]
4a	C_6H_5	4-$(CH_3)_2NC_6H_4$	73	100:0
4a[c]	C_6H_5	4-$(CH_3)_2NC_6H_4$	80	100:0
4b	$C_6H_5CH_2$	4-$(CH_3)_2NC_6H_4$	60	100:0
4c	C_6H_5	4-$CH_3OC_6H_4$	88	94:6
4d	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	81	93:7
4e	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	73	92:8
4f	$C_6H_5CH_2$	4-$CH_3OC_6H_4$	73	92:8
4g	4-$CH_3OC_6H_4$	$C_6H_5CH{=}CH$	46	55:45
4h	C_6H_5	4-FC_6H_4	88	50:50
4i	C_6H_5	c-C_6H_{11}	83	33:67
4j	C_6H_5	4-$NO_2C_6H_4$	75	18:82
4k[c]	C_2H_5	4-$CH_3OC_6H_4$	80	88:12

[a] Isolated yields. [b] The ratios of (*E*)- and (*Z*)-isomers were estimated on the basis of NMR data. [c] The reaction was catalyzed by CuBr−H_2O.

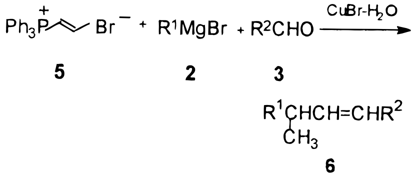
The reaction of PhMgBr with vinyltriphenylphosphonium bromide in the presence of CuBr was successful, but the yield was low (25%) when either a catalytic or equivalent amount of CuBr was used.

Further experiments showed that the reaction proceeded more efficiently in the presence of a catalytic amount of CuBr−Ag_2CO_3.

The results are summarized in Table 1.

A variety of Grignard reagents and aldehydes could be used in this reaction. The results are summarized in Table 2.

Attempts to use alkyl Grignard reagents in this reaction failed. However, we found that either alkyl or aryl Grignard reagents did react with 1-propenyltriphenylphosphonium bromide in the presence of CuBr−H_2O. The results are summarized in Table 3.



Similarly either alkyl or aryl Grignard reagents reacts with vinyltriphenylphosphonium bromide in the presence of CuBr−H_2O. The results are summarized in Table 2 (**4a**[c] and **4k**).

The effect of additives as well as reaction time and temperature has been investigated. The results are summarized in Tables 3 and 4. It is obvious that the

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S0022-3263(96)00899-7 CCC: $12.00

Table 3. Reactions of Grignard Reagents with 5 Followed by Addition of 3 Catalyzed by CuBr−H_2O

compd	R^1	R^2	yield (%)[a]	(*E*):(*Z*)[b]
6a	C_6H_5	4-$(CH_3)_2NC_6H_4$	90	100:0
6b	*n*-C_4H_9	4-$(CH_3)_2NC_6H_4$	75	100:0
6c	$C_6H_5CH_2$	4-$(CH_3)_2NC_6H_4$	70	100:0
6d	*n*-C_4H_9	4-FC_6H_4	90	60:40
6e	$C_6H_5CH_2$	piperyl	94	55:45
6f	$C_6H_5CH_2$	4-FC_6H_4	87	40:60
6g	C_6H_5	4-ClC_6H_4	82	33:67
6h	*n*-C_4H_9	4-ClC_6H_4	82	30:70
6h[c]	*n*-C_4H_9	4-ClC_6H_4	68	18:82
6h[d]	*n*-C_4H_9	4-ClC_6H_4	10	10:90
6i	C_6H_5	3-$NO_2C_6H_4$	84	14:86

[a] Isolated yields. [b] The ratios of (*E*)- and (*Z*)-isomers were estimated on the basis of NMR data. [c] The reaction was carried out at 0−70 °C for 10−30 min. [d] The reaction was carried out at −70 °C for 90 min.

Table 4. Effect of the Amounts of CuBr and Water

run	compd	CuBr (mol %)	H_2O (μL)	yield (%)[a]
1	**4k**	22	0	0
2	**4k**	22	4	80
3	**4k**	22	8	50
4	**6g**	22	4	82
5	**6g**	11	4	53
6	**6g**	0	4	16
7	**6g**	22[b]	4	85

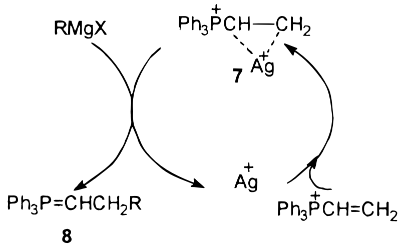
[a] Isolated yields. [b] Using 22 mmol % of CuCl as catalyst.

yield decreased and the stereoselectivity improved as the reaction temperature was decreased (Table 3, **6h**, **6h**,[c] and **6h**[d]).

Although the mechanistic aspects are not clear at present, the following parameters play important roles.

(1) Copper(I) Catalyst. Either CuBr or CuCl could be used in this reaction as a catalyst (Table 4).

(2) Silver Carbonate. A number of coadditives, such as Ag_2CO_3, LiCl, $ZnCl_2$, $CoCl_2$, $FeCl_3$, MoO_3, and Cp_2TiCl_2, were tested, but silver carbonate was the only compound that showed catalytic activity. When silver carbonate was used alone, no reaction took place (Table 1, run 2). In the case of CuBr−Na_2CO_3, the yields were low (Table 1, run 3). It seems that silver salts may play an important role[8] as follows.



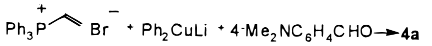
(3) Trace of Water. Attempts to carry out this reaction in DMF or CH_2Cl_2 failed. Although in these solvents the solubility of the vinylic phosphonium salts increased, the solvents themselves reacted with the Grignard reagent[9] resulting in the formation of a number of byproducts. Thus THF was used as the solvent. Presumably the reaction takes place at the surface of the insoluble vinylic phosphonium salts. A trace of water absorbed on the interface would increase the solubility of these salts in THF. This in turn should increase the rate and yield of the reaction. However, excessive water could react with the Grignard reagent leading to decreased yields (Table 4, run 3).

Table 5

run	nucleophile	yield (%)	(*E*):(*Z*)
1	Ph_2CuLi	60	45:55
2	PhMgBr	90	100:0

It has been reported that[10] cuprates react with vinyltriphenylphosphonium bromide; the resulting phosphoranes react with aldehydes to give alkenes as a mixture of (*Z*)- and (*E*)-isomers. The stereoselectivity could be changed significantly by the addition of hexamethylphosphoramide (HMPA), a highly toxic cancer suspect agent.

We have repeated the cuprate method for comparsion with our results and found that, in the case examined, our method gave a higher yield and was more stereoselective as shown in Table 5.



In conclusion, the consecutive reaction of vinylic phosphonium salts with a variety of Grignard reagents and aldehydes to form substituted alkenes ($R^1CH_2CH{=}CHR^2$ or $R^1CH(CH_3)CH{=}CHR^2$) is catalyzed by CuBr−Ag_2CO_3 or CuBr−H_2O. The stereoselectivity depended on the nature of substituents in the benzene ring of the aldehydes. Electron-donating groups increase the (*E*)-selectivity, whereas the reverse is true for electron-withdrawing groups. We have not yet formulated a reasonable explanation for these results. However, the method provides a direct route to various substituted styrenes and represents an improvement over previous related routes.[10]

Experimental Section

General. Mass spectra were obtained by chemical ionization, and the mass spectra are reported as *m*/*e* (relative intensity). All reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen. Solvents were removed under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column. The ratios of (*E*)- and (*Z*)-isomers were estimated on the basis of NMR data. The experimental error is <5% from duplicate experiments.

General Procedure for the Preparation of Substituted Alkenes 4. Grignard reagent **2** (1.5 mmol) was added dropwise to a suspension of vinyltriphenylphosphonium bromide (**1**) (1.36 mmol), CuBr (0.28 mmol), and Ag_2CO_3 (0.04 mmol) in THF (10 mL) at −78 °C under nitrogen. After the addition of **2**, the reaction mixture was allowed to reach to −40 °C and stirred for 1 h. Then the aldehyde **3** (0.87 mmol) was added, and the temperature was warmed to 20 °C within 4 h. After letting the mixture stand overnight, the mixture was diluted with 30 mL of ether, water was added, and the organic layer was separated and dried. Removal of the solvent gave a residue which was purified by chromatography with petroleum ether−ethyl acetate (100:2) as the eluting solvent.

3-Phenyl-1-(4-(*N*,*N*-dimethylamino)phenyl)-1-propene (4a). Yield: 73%; mp 48−50 °C. IR(KCl): 1620, 1500, 1360, 960 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.95 (s, 6H), 3.52 (d, 2H, $J = 6.7$ Hz), 6.09−6.25 (m, 1H), 6.40 (d, 1H, $J = 15.7$ Hz), 6.68−7.38 (m, 9H) ppm. MS: 237 (M^+, 100), 236 (37), 193 (11), and 115 (17). Anal. Calcd for $C_{17}H_{19}N$ (237.34): C, 86.03; H, 8.07; N, 5.90. Found: C, 86.03; H, 8.09; N, 5.78.

General Procedure for the Preparation of Alkenes 6. A suspension of 1-propenyltriphenylphosphonium bromide (**5**) (1.3 mmol), CuBr (0.28 mmol), THF (10 mL), and water (4 μL) was stirred at 0 °C under nitrogen for 5 min, and the Grignard reagent **2** (1.6 mmol) was added dropwise. After addition of the

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Grignard reagent, the reaction mixture was stirred at 0−10 °C for 0.5 h and the aldehyde **3** (0.87 mmol) was added. After the mixture was stirred overnight, the mixture was diluted with diethyl ether (30 mL) and water, and the organic layer was separated and dried. Removal of the solvent gave a residue which was purified by chromatography with petroleum ether−ethyl acetate (100:2) as the eluting solvent.

3-Phenyl-1-(4-(*N*,*N*-dimethylamino)phenyl)-1-butene (6a). Yield: 90%; bp 120 °C/1 mmHg. IR(neat): 1600, 1500, 1440, 980 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.42 (d, 3H, $J = 7.0$ Hz), 2.92 (s, 6H), 3.50−3.61 (m, 1H), 6.18 (dd, 1H, $J = 6.7, 15.8$ Hz), 6.32 (d, 1H, $J = 15.8$ Hz), 6.65−7.30 (m, 9H) ppm. MS: 251(M^+, 100), 236 (81), 221 (7), 191 (7), 91 (8). Anal. Calcd for $C_{18}H_{21}N$ (251.37): C, 86.01; H, 8.42; N, 5.57. Found: C, 85.84; H, 8.47; N, 5.71.

Acknowledgment. We thank the National Natural Science Foundation of China, the Laboratory of Organometallic Chemistry, and Academia Sinica for financial support.

Supporting Information Available: Characterization and analytical data of compounds **4b**−**k** and **6b**−**i** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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